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How are arbovirus vectors able to tolerate infection?

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Abstract:

One of the defining features of mosquito vectors of arboviruses such as Dengue and Zika is their ability to tolerate high levels of virus proliferation without suffering significant pathology. This adaptation is central to vector competence and disease spread. The molecular mechanisms, pathways, cellular and metabolic adaptations responsible for mosquito disease tolerance are still largely unknown and may represent effective ways to control mosquito populations and prevent arboviral diseases. In this review article, we describe the key link between disease tolerance and pathogen transmission, and how vector control methods may benefit by focusing efforts on dissecting the mechanisms underlying mosquito tolerance of arboviral infections. We briefly review recent work investigating tolerance mechanisms in other insects, describe the state of the art regarding the mechanisms of disease tolerance in mosquitos, and highlight the emerging role of gut microbiota in mosquito immunity and disease tolerance.

Keywords: mosquito; arbovirus; disease-tolerance.

Introduction:

Diseases caused by mosquito-borne arboviruses like Dengue, Zika, Chikungunya, Yellow Fever, West Nile (WNV), Mayaro and Japanese Encephalitis (JEV), are important sources of worldwide morbidity and mortality. Dengue fever alone affects more than 390 million people every year in tropical and sub-tropical areas of the world (Bhatt et al. 2013). In the absence of an efficient vaccine, and faced with the emergence of insecticide resistant mosquito strains, it is important to explore alternative avenues of vector control. One approach is to focus on the behavioral and physiological determinants of vectorial competence, including how mosquitoes maintain homeostasis and fitness while infected with arbovirus, and how this trait influences disease transmission. If we understand what makes a good vector, we may begin to uncover new ways to reduce or even disrupt vectorial capacity.

A fundamental feature of mosquito-virus interactions is that following the ingestion of an infectious blood meal there is proliferation and spread of virus particles from the mosquito midgut to the salivary glands. During this process, mosquitoes often experience minimal physiological and fitness costs associated with arbovirus replication (Moreno-Garcia et al., 2014; Shaw et al., 2018), highlighting how mosquito vectors are tolerant to arbovirus infection (Lambrechts and Saleh, 2019). Although some work has reported different degrees of fitness costs to mosquitoes during arbovirus infection (Lambrechts and Scott, 2009; Grubaugh et al., 2017; Petersen et al., 2018; Silveira et al., 2018), virus proliferation is frequently non-pathogenic and the observed harm is host and pathogen strain-specific (Martin et al., 2010; Reiskind et al., 2010; Tesla et al., 2018; Sirisena et al., 2018).

Disease tolerance is a host defense strategy to maximize homeostasis and fitness independent of mechanisms that kill microbes. It acts in concert with other evolutionary conserved defensive strategies, such as immune resistance (killing microbes) and behavioral avoidance (reducing the risk of infection). The ability to tolerate a viral infection is no doubt an essential attribute of an effective disease vector. Given the prevalence of insect-vector human pathogens, it is striking that we currently know so little about how mosquitos are able to tolerate infection by

the viruses they vector, and how this ability varies in natural mosquito populations (Dharmarajan et al., 2019). By understanding the metabolic and molecular mechanisms that promote disease tolerance in mosquitoes, we may uncover novel targets to reduce vector competence and block virus transmission to humans.

The link between tolerance and transmission:

Organisms have evolved a variety of behavioral and physiological strategies to avoid, clear or tolerate infections. Immune-mediated pathogen killing is a well-studied strategy that contributes to disease resistance. Acting independently or in cooperation with mechanisms that kill pathogens, immune-metabolic and physiological responses to infection may also promote tissue protection or repair, preserving host homeostasis during infection (Martins et al., 2019; Ganeshan et al., 2019). These responses secure host health and recovery independently of pathogen killing, and so they are likely to promote disease tolerance, allowing hosts to maintain a relative level of health despite harboring relatively high pathogen burdens (see Box 1). The concept of health is directly connected to homeostasis and the ability to maintain animal physiologies operating properly at the cellular, tissue and systemic levels (Buchman, 2002; Chovatiya and Medzhitov, 2014).

While disease tolerance may improve host health at the individual level, because infectious hosts remain alive and healthy for longer, one potential population-level consequence of elevated disease tolerance is an increase in the prevalence of infection (Miller et al., 2005; Read et al., 2008; Vale et al., 2014). Beyond this intuitive reasoning, there is evidence from both theoretical and experimental approaches that reducing the severity of disease in the host (increasing disease tolerance) can lead to increased spread and prevalence of infection (Hozé et al., 2018; Read et al., 2015; Vale et al., 2014). For example, environmental conditions conducive to greater disease tolerance have been found to foster super-shedding individuals who contribute disproportionately more to the total transmission (Vale et al., 2013, 2011), while therapeutic interventions that boost host tolerance are predicted to increase the prevalence of infections (Hozé et al., 2018; Vale et al., 2014), mainly through the impact of increasing host lifespan,

and consequently, the infectious period. To fully grasp the consequences of disease tolerance for pathogen spread, it is therefore important to quantify the extent of natural variation in infection tolerance, and test if more tolerant individuals have greater potential for disease transmission (Henschen and Adelman, 2019; Vale et al., 2013).

How do organisms tolerate infection?

Understanding the physiological mechanisms underlying disease tolerance phenotypes in mosquitos would be helpful in designing therapeutic interventions that aim to reduce their tolerance to vectored pathogens as a means of reducing their vectorial competence (Shaw et al., 2018). The most obvious candidates for such mechanisms are those which either prevent tissue damage from occurring or that are central in the process of repairing tissue damage (Martins et al., 2019; Soares et al., 2017, 2014). Mechanisms that target secreted virulence factors or toxins, for example, are good candidates for tolerance mechanisms because they can prevent pathology without directly eliminating pathogens (Allen et al., 2014; Rasko and Sperandio, 2010; Vale et al., 2014). Disease severity is also directly affected by immunopathology induced during prolonged or unregulated inflammatory responses to pathogens, and therefore anti-inflammatory mechanisms are equally promising mechanisms of disease tolerance (Ayres and Schneider, 2012; Martins et al., 2019; Vale et al., 2014). Finally, once damage has occurred, more tolerant hosts are likely to repair tissue damage and recover from infection. Our understanding of how mosquito vectors tolerate infection would therefore be greatly enhanced by focusing our efforts on mechanisms that promote physiological integrity, reduced inflammation and enhanced tissue damage repair. However, we currently have a limited understanding of the physiological and immune mechanisms that allow arthropod vectors to tolerate infection. Since arbovirus infection and transmission by mosquitoes are closely associated with hematophagy, the metabolic adaptations triggered by the pro-oxidant nature of the blood meal (Sterkel et al., 2017) are likely to modulate mosquito disease tolerance to arbovirus.

What can other insects teach us about disease tolerance mechanisms in mosquito vectors?

Disease tolerance has been well studied in plants (Baucom and de Roode 2011) and more recently in animals (Råberg et al. 2009; Ayres and Schneider 2008; Baucom and de Roode 2011; Vale and Little 2012). In invertebrates, most research has focused on bacterial or viral infections in *Drosophila* (Brandt et al. 2004; Ayres and Schneider 2008; Teixeira 2012) or bacterial infections in the freshwater crustacean *Daphnia* (Vale et al. 2011; Vale and Little 2012), and protozoan infections in Monarch butterflies (Lefèvre et al. 2011; Sternberg et al. 2013). Despite the obvious differences between the physiology of hematophagous vectors and other ecologically distinct hosts, there is substantial evolutionary conservation in immune and tissue repair mechanisms that mediate the response to many infections (Hoffmann et al., 1999). One potentially helpful approach may therefore be to leverage work done in other model systems of infection, particularly insects, to identify potential candidate mechanisms of disease tolerance in mosquito vectors (Gupta and Vale, 2017; Howick and Lazzaro, 2014; Lissner and Schneider, 2018; Louie et al., 2016; Sternberg et al., 2012; Troha et al., 2018).

For example, a recent comparison of transcriptional profiles in *Drosophila* infected with a range of bacterial pathogens identified the transcription factor CrebA which, when knocked down, resulted in reduced tolerance due to increased cellular stress (Troha et al., 2018). Other work in *Drosophila* measured tolerance to bacterial infection in a panel of inbred lines and identified several candidate genes associated with variation in disease tolerance (Howick and Lazzaro, 2017). Among them, *grainy head* (*ghd*) is shown to be involved in epithelial wound repair via embryonic ERK pathway signaling, and *debris buster* (*dsb*) is previously implicated in autophagy of cellular debris (Han et al., 2014; Howick and Lazzaro, 2017; Mace et al., 2005). These two studies highlight that the maintenance of cellular homeostasis in addition to tissue damage repair may be central to disease tolerance in insects.

Other work in *Drosophila* has also shed light on how immune regulation mechanisms may play an important role in disease tolerance. The epigenetic regulator of the JAK-STAT pathway G9a, for example, has been identified as being

important in tolerating systemic infection by Drosophila C Virus, mainly due its role in downregulating immunopathology during viral infection (Merkling et al., 2015). Interestingly, G9a appears to have greater effects in male flies, and affects tolerance not by reducing the overall severity of infection, but by changing the sensitivity of flies to increasing concentrations of DCV (Gupta and Vale, 2017). Future work may therefore benefit from focusing on negative regulators of immune responses as key mediators of disease tolerance.

Mechanisms of disease tolerance to arbovirus infection in mosquitoes:

Several immune signaling pathways are activated in mosquitoes during arboviral infections, such as the antiviral RNAi (Sanchez-Vargas et al., 2009; Olmo et al., 2018), JAK-STAT (Souza-Neto et al., 2009), Toll (Xi et al., 2008), and IMD (Barletta et al., 2017) pathways. The inhibition of specific components of immune resistance, such as RNAi, leads to viral over proliferation and host mortality, demonstrating that controlling viral growth is essential for mosquito defense (Myles et al., 2008; Cirimotich et al., 2009). Despite that, antiviral immune resistance operates at low to moderate levels. Arbovirus titers increase 100 to 1000-fold in mosquito bodies following an infectious blood meal and Dengue, for example, can establish persistent lifelong infections (Salazar et al., 2007). This lower state of immune resistance maintains viral burden under an acceptable homeostatic range for the vector, but is only possible because mosquitoes rely on complementary defensive strategies that prevent arbovirus-triggered pathology. Below, we briefly describe some known mechanisms involved in vector disease tolerance, including the role of gut microbiota in the modulation of vector competence (Box 2).

Cellular renewal and homeostasis. Cell death and regeneration determine disease tolerance in different systems through the modulation of tissue composition and integrity (Jamieson et al., 2013; Sahoo et al., 2014; Soares et al., 2017). In mosquitoes, apoptosis impacts vector competence leading to antagonistic outcomes depending on arbovirus and insect species. *Aedes aegypti* strains refractory to Dengue have increased expression of pro-apoptotic genes and higher numbers of midgut apoptotic cells during infection (Ocampo et al., 2013, Eng et al., 2016) and

the induction of apoptosis controls Sindbis spread, collectively suggesting mosquito cell death can restrict arbovirus (O'Neill et al., 2015). Paradoxically, inhibiting apoptosis through silencing of the initiator caspase Aedronc decreased Dengue virus load and dissemination (Eng et al., 2016) and activating apoptosis using RNAi-mediated silencing of the anti-apoptotic gene iap1 increased Sindbis infection (Wang et al., 2012). To compensate for the loss of apoptotic cells that could compromise tissue integrity, damage caused by chemical or infectious insults trigger an adaptive response leading to cell regeneration and reestablishment of midgut homeostasis (Janež et al., 2017). In the context of Dengue infection, the proliferation of intestinal stem cells (ISC) is delayed in susceptible *A. aegypti* Rockefeller strain, suggesting that midgut cell renewal may regulate vector competence (Taracena et al., 2018). So far, it is not clear how cell turnover influences mosquito-virus interactions and we can only speculate that the interplay between infection-induced apoptosis and the compensatory ISC proliferation is likely to contribute to tissue integrity, midgut homeostasis and vector disease tolerance. In a recent study, Thaker and collaborators (2019) compared metabolic alterations induced by Zika in mosquito versus human cell and revealed an energy depletion that led to AMPK activation and apoptosis in humans but not mosquito cells, which, if confirmed in whole insects, could help to explain the tolerance phenotype of infected mosquitoes (Figure 2).

Reducing viral pathology. The neutralization of arbovirus-induced pathology in mosquitoes is essential for disease transmission. Some flavivirus, such as Dengue and Zika, show neurotropism for mosquito nervous system, including the brain, and promote behavioral alteration in infected females (Zhang et al., 2010; Lima-Camara et al., 2011; Gaburro et al., 2018). The neural factor Hikaru genki of *A. aegypti* (AeHig) is expressed in the nervous system and promotes disease tolerance by restricting neuronal apoptosis and arbovirus damage to mosquito brains, preventing lethal infections following arbovirus-contaminated blood meals (Xiao et al., 2015).

Modulation of arboviral persistent infections: Insect cells and mosquitoes infected with arbovirus, such as Dengue, Chikungunya, Zika and West Nile, produce

viral DNA fragments (vDNA) that integrate into mosquito genomes, known as endogenous viral elements (EVEs) (Crochu et al., 2004, Nag et al., 2016 and 2017). vDNA synthesis is mediated by the reverse transcriptase activity of mosquito transposons, uses defective viral genomes as templates and is modulated by Dicer-2 (Poirier et al., 2018). EVEs can be either incomplete or contain functional open reading frames of several arbovirus (Suzuki et al 2017; Palatini et al., 2017) inserted into a genomic loci rich in transposable elements called piRNA clusters (Arensburger et al., 2011; Whitfield et al., 2017). Transcripts derived from EVEs inserted into piRNA clusters activate the piRNA pathway, which is expanded in *Aedes* mosquitoes, to generate virus-derived piRNAs (vpiRNAs) that contribute to mosquito antiviral resistance (Morazzani et al., 2012; Schnettler et al., 2013; Miesen et al., 2015; Miesen et al., 2016). vDNA also mediates persistent viral infections in mosquitoes, potentially connecting its synthesis to vector disease tolerance (Goic et al., 2016) (Figure 2). *Aedes albopictus* infected with Chikungunya and treated with AZT, an inhibitor of reverse transcriptase, had reduced vDNA levels and increased vector mortality following infection without alterations in viral loads, suggesting that arboviral disease tolerance is dependent on the formation of vDNA (Goic et al., 2016). How vDNA is involved in the establishment of viral persistent infections and vector disease tolerance awaits further investigations.

Conclusion and perspectives:

After feeding on virus-contaminated blood, vector mosquitoes support intense virus proliferation without major homeostatic imbalances, being tolerant to arbovirus. Targeting tolerance-promoting pathways have the potential to decrease vector competence due to reduction in mosquito health and fitness, ultimately affecting the number of infectious bites and/or vector lifespan. By learning how mosquitoes tolerate infection we may uncover potential therapeutic targets to inhibit vector tolerance, inducing mosquito mortality and disrupting arbovirus transmission.

Box 1 - Measuring tolerance: the relationship between health and pathogen load

When comparing two different groups or populations of hosts, a common approach is to analyze how host health changes with increasing infection loads for each of the groups of interest (Raberg et al., 2007). In its simplest form, this relationship may be linear, and host groups showing steep negative slopes for this reaction norm suffer a loss in health with increasing loads, while hosts with flat reaction norms are able to maintain health even as pathogen loads increase, and are therefore relatively tolerant (Figure 1a).

Depending on the nature of the data, more complex non-linear relationships are also possible, as has been shown in viral and bacterial infections in *Drosophila* (Gupta and Vale, 2017; Howick and Lazzaro, 2014; Louie et al., 2016) and in HIV infection in humans (Regoes et al., 2014). In these cases, a non-linear logistic model may be more appropriate (Figure 1b). This type of model goes beyond the analysis of the rate of health loss with increasing pathogen loads, providing information about how groups of hosts may differ in various parameters of the response to infection, including their vigor in the absence of infection, sensitivity to increases in pathogen load (affecting the lethal load of infection) or the severity of infection, which determines how sick a host can get during infection, including ultimate death (Figure 1b) (Louie et al., 2016).

An important consideration in both linear and non-linear analyses is that they require both health and pathogen load to be measured on the same individuals (each data-point in the correlation must correspond to one individual host). This is often not possible when obtaining these data since it requires destructive sampling of the individual host, which is often the case in mosquitos and other invertebrates. In these cases, it is still possible to measure tolerance as the average health of a group of hosts relative to the average pathogen load of the same group (Figure 1c). For example, genotype-specific measures of survival and pathogen loads could be useful to distinguish differences in tolerance among distinct genetic backgrounds of mosquito, even if survival and pathogen loads are measured in different groups of insects.

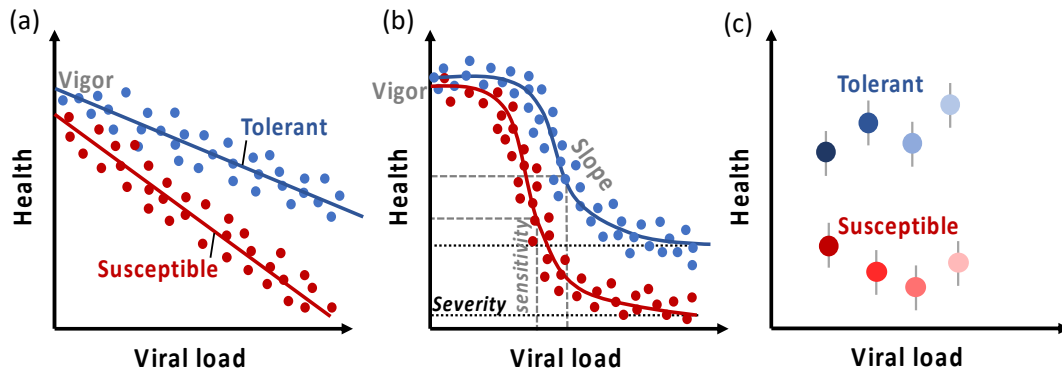


Figure 1: A tolerance curve is a tool to quantify disease tolerance in distinct populations. The shape of tolerance curves allows distinct interpretations of host – pathogen interactions: (a) In linear tolerance curves it is possible to measure vigor (health of uninfected individuals) and the slope of health loss over an infectious gradient. However, the relationship between host health and pathogen load is often not best described by a linear model, and using a sigmoid model as seen in (b) with the 4-parameter logistic model (vigor, slope, sensitivity and severity) allows a better analysis of infection dynamics. (c) “Point tolerance” describes different tolerance properties of populations where health and viral loads were measured in distinct pools of infected hosts.

Box 2 – Gut microbiota and the modulation of vector competence

The intestinal microbiota of insects plays an important role in several host processes, including gut cell renewal and growth (Buchon et al., 2009; Shin et al., 2011); nutrient breakdown and supplementation (Warnecke et al., 2007; Hongoh et al., 2008; Nikoh et al., 2011) and toxin catabolism, among others (Kikuchi et al., 2012; Ping et al., 2007). Given its profound relationship with host physiology, it is likely that vector microbiota also modulates disease tolerance, as shown in non-insect models (Ripert et al., 2016; Rangan et al., 2016; Ayres, 2016). In the following paragraphs, we discuss how the microbiota influences pathogen colonization and vector competence by enhancing or inhibiting the presence of gut pathogens.

The composition of the vector's intestinal microbiota is fundamental in regard to its ability (competence) to transmit pathogens to humans (Ramirez et al. 2014, Bahia et al., 2014). This was illustrated in studies with *Anopheles gambiae* and *A. aegypti* where the removal of bacteria from the insect's midguts with antibiotics increased parasitemia with *Plasmodium* spp. and dengue virus (Dong et al., 2009; Xi et al., 2008) through different mechanisms (Saraiva et al., 2016). The microbiota shapes peritrophic matrix formation and influences innate immune system activation (Rodgers et al., 2017). The microbiota proliferation after blood meal induces the IMD immune pathway and antagonizes virus infection (Barletta et al., 2017). The caudal transcription factor, a negative regulator of IMD, facilitates microbiota tolerance by down-regulating REL2-dependent expression of antimicrobial peptides, specifically in the gut, thereby enabling microbiota establishment (Clayton et al., 2013).

The insects' gut *Enterobacter* sp. bacterium secretes reactive oxygen species that kills *Plasmodium* in the gut lumen of *Anopheles* mosquitoes (Cirimotich et al., 2011). *Chromobacterium* sp. secretes a neutral protease and an aminopeptidase that degrade the viral envelope (E) protein and thus inhibit viral attachment and subsequent infection of *A. aegypti* cells (Ramirez et al., 2014; Saraiva et al., 2018a). The *Chromobacterium* sp. also has *in vivo* and *in vitro* anti-*Plasmodium* properties through secretion of romidepsin (Ramirez et al., 2014; Saraiva et al., 2018b).

By contrast, the microbiota may instead facilitate pathogen replication. The susceptibility of *A. aegypti* to Dengue virus infection increases significantly after *Serratia odorifera* gut colonization (Apte-Deshpande et al., 2012). Similarly, the *Penicillium chrysogenum* fungus makes *A. gambiae* more susceptible to *Plasmodium* infection through the upregulation of mosquito ornithine decarboxylase gene that sequesters arginine, a substrate for the microbicidal radical nitric oxide production (Angleró-Rodríguez et al., 2016). In a similar fashion, *Talaromyces* sp. isolated from field-collected *A. aegypti* facilitates Dengue virus infection by down-regulating digestive enzyme genes and trypsin activity (Angleró-Rodríguez et al., 2017). The introduction of *Serratia marcescens* in antibiotic-treated *A. aegypti* facilitates dengue virus dissemination and transmission through secretion of enhancin, which digests mucins of the mosquito's mucus layer (Wu et al., 2019).

The contribution of microbiota for the host's disease tolerance response is still poorly explored and future work is needed to elucidate its influence in insect immune modulation, vectorial competence and pathogen transmission.

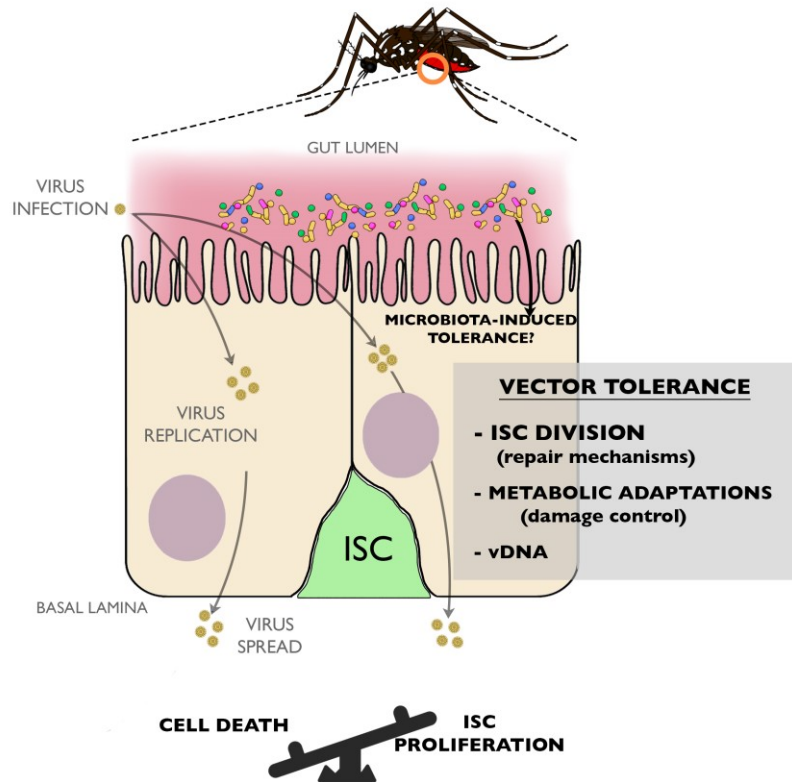


Figure 2: Possible tolerance mechanism operating in mosquito midgut during the first days following an infectious blood meal. Mechanisms driving mosquito disease tolerance to arbovirus infection may involve pathways that prevent molecular damage (damage control) and pathways that lead to organelle, cell and tissue repair once damage has occurred. It is possible that these pathways are also active in other tissues, such as brain, flight muscle, fat body, salivary glands and ovaries. Virus infection and replication in midgut epithelium will likely drive an adaptive tolerance response involving a balance between cell death and intestinal stem cell (ISC) division in order to keep gut integrity and homeostasis. At the same time, cellular energy reserves acting as stress sensors promote metabolic adaptations and virus-derived DNA (vDNA) is produced and promotes disease tolerance during infection. Several other mechanisms such as microbiota-induced tolerance are possible but, so far, still lack empirical evidence.

Box 3 – Outstanding questions in disease tolerance of arbovirus vectors

- How much do vectors vary in tolerance phenotypes within natural mosquito populations?
- How do mosquitos tolerate different viral pathogens?
- How do cellular renewal and vDNA contribute to vector disease tolerance?
- Are there fitness costs to the mosquito in tolerating viral infection (reduced fecundity/lifespan)?
- Is there a role for mosquito gut microbiota in the ability to tolerate arbovirus infections?

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